JACC Vol. 14, No. 1
July 1989:219–24

EXPERIMENTAL STUDIES

Cardioprotective Effects of Various Class I Antiarrhythmic Drugs in Canine Hearts

YOSHIHIRO HANAKI, MD, SATORU SUGIYAMA, MD, PHD,* NOBUYUKI HIEDA, MD, PHD,* KAZUMI TAKI, MD, PHD,† HIROSHI HAYASHI, MD, PHD, TAKAYUKI OZAWA, MD, PHD*

Nagoya, Japan

This study was designed to clarify the cardioprotective effects of various class I antiarrhythmic drugs, i.e., aprindine, disopyramide, flecainide, lidocaine, mexiletine, pentisomide and propafenone, on the ischemic heart. Sixty-one adult mongrel dogs were classified into eight groups according to premedication: 1) control group, physiologic saline solution was administered intravenously 25 min before left anterior descending coronary artery ligation; 2) aprindine group, 3 mg/kg body weight of aprindine intravenously; 3) disopyramide group, 2 mg/kg of disopyramide intravenously; 4) flecainide group, 2 mg/kg of flecainide intravenously followed by drip infusion of 100 μg/kg per min; 5) lidocaine group, 2 mg/kg of lidocaine intravenously followed by drip infusion of 100 μg/kg per min; 6) mexiletine group, 3 mg/kg per min of mexiletine intravenously followed by drip infusion of 15 μg/kg per min; 7) pentisomide group, 5 mg/kg intravenously; and 8) propafenone group, 2 mg/kg intravenously. Arterial blood pressure and electrocardiogram were monitored throughout the experiment.

Two hours after coronary occlusion, the heart was excised. Myocardial mitochondria were prepared and mitochondrial function (the respiratory control index and the rate of oxygen consumption in state III) was measured polarographically. Fractionation of myocardial tissues was performed and the lysosomal enzyme (N-acetyl-β-glucosaminidase and β-glucuronidase) activities among fractions were measured.

No significant hemodynamic changes were observed compared with the control group except for those in the disopyramide and flecainide groups; that is, decrease in heart rate without changes in blood pressure compared with the control group was observed.

All antiarrhythmic drugs effectively prevented the development of ventricular arrhythmias associated with ischemia. Two hours of coronary occlusion induced mitochondrial dysfunction and leakage of lysosomal enzymes. In contrast, each antiarrhythmic drug without exception lessened mitochondrial dysfunction and prevented the leakage of lysosomal enzymes concomitantly. These results indicate that class I antiarrhythmic drugs have cardioprotective effects on ischemic myocardium.

(J Am Coll Cardiol 1989;14:219–24)

Ventricular arrhythmias in patients with acute myocardial infarction are significant clinical challenges. Immediate recognition of rhythm disturbances, appropriate assessment of precipitating factors and prompt initiation of appropriate therapy are crucial in the management of arrhythmias. Advances in electrophysiology contribute significantly to clarifying the genesis and management of arrhythmias. Several biochemical derangements have been implicated in the genesis of arrhythmias related to acute ischemia (1). Accordingly, it is deduced that lessening of the severity of ischemia is closely related to improvement of predisposing conditions for lethal arrhythmias. Beta-adrenergic blockers, class II and calcium channel antagonists, class IV antiarrhythmic drugs have cardioprotective effects on the ischemic heart (2–5). Furthermore, recent studies (6) revealed that amiodarone, a class III antiarrhythmic drug, protects myocardial mitochondria against ischemia. In addition, it is reported (7,8) that cardioprotective drugs, which are not classified as class I to IV antiarrhythmic drugs, showed an antiarrhythmic effect on the ischemic heart. Therefore, the relation between antiarrhythmic effect and cardioprotective effect has attracted much interest. Nevertheless, little information is available concerning the biochemical effects of class I antiarrhythmic drugs, the most widely used antiarrhythmic agents, on the ischemic heart (9).

In this study, we estimated the cardioprotective effects of various class I antiarrhythmic drugs on the ischemic heart by

From the Departments of Internal Medicine,*Biomedical Chemistry and †Anesthesiology, Faculty of Medicine, University of Nagoya, Nagoya, Japan.

Manuscript received October 24, 1988; revised manuscript received January 4, 1989, accepted February 2, 1989.

Address for reprints: Takayuki Ozawa, MD, Department of Biomedical Chemistry, Faculty of Medicine, University of Nagoya, Tsuruma, Showa-ku, Nagoya, 466, Japan.

0735-1097/89/$3.50

JACC Vol. 14, No. 1
July 1989:219–24

measuring changes in mitochondrial function and leakage of lysosomal enzymes as biochemical markers in the ischemic heart.

Methods

Animal preparation. Sixty-one adult mongrel dogs of either gender, weighing 7 to 12 kg, were anesthetized with sodium pentobarbital (50 mg/kg body weight) intraperitoneally. The dogs were intubated and ventilated with a Harvard type respirator (Igarashi Ika Kogyo). Lead II of the electrocardiogram (ECG) was monitored continuously throughout the experiment by a VC-640G oscillographic recorder (Nihon Kohden) and recorded simultaneously by an ICR-7200 ambulatory ECG recorder (Nihon Kohden). Catheters were placed in the right femoral artery and vein for monitoring aortic blood pressure (AD-600, Nihon Kohden) and for administration of drugs and adequate hydration, respectively. A left thoracotomy was performed in the fourth or fifth intercostal space, and the heart was suspended in a pericardial cradle. The left anterior descending coronary artery immediately distal to the first diagonal branch was dissected free and a silk suture was placed around the coronary artery for acute occlusion. Two hour occlusion was performed by ligating the vessel. The experiments performed conform to the Position of the American Heart Association on Research Animal Use adopted November 11, 1984 by American Heart Association.

Experimental design. The 61 dogs were classified into eight groups. In the control group (n = 12), physiologic saline solution was administered intravenously throughout the experiment. In the aprindine group (n = 7), 25 min before coronary occlusion, 3 mg/kg of aprindine hydrochloride dissolved in 25 ml of saline solution was administered intravenously for 10 min. In the disopyramide group (n = 7), 25 min before coronary occlusion, 2 mg/kg of disopyramide hydrochloride dissolved in 25 ml of saline solution was administered intravenously for 10 min. In the flecainide group (n = 7), 25 min before coronary occlusion, 2 mg/kg of flecainide acetate dissolved in 5 ml of distilled water was administered intravenously for 10 min followed by a constant infusion of 100 μg/kg per min dissolved in water (20 ml) with use of an infusion pump. In the lidocaine group (n = 7), 25 min before occlusion, 2 mg/kg of lidocaine hydrochloride dissolved in 5 ml of saline solution was administered intravenously for 10 min followed by a constant infusion of 100 μg/kg per min dissolved in saline solution (20 ml) with use of an infusion pump. In the mexiletine group (n = 7), 3 mg/kg of mexiletine hydrochloride dissolved in 5 ml of saline solution was administered intravenously for 10 min followed by a constant infusion of 15 μg/kg per min dissolved in saline solution (20 ml) with use of an infusion pump. In the pentisomide group (n = 7), 25 min before coronary occlusion, 5 mg/kg of pentisomide dissolved in 25 ml of water was administered intravenously for 10 min. In the propafenone group (n = 7), 25 min before coronary occlusion, 2 mg/kg of propafenone dissolved in 25 ml of water was administered intravenously for 10 min.

Hemodynamic measurements. Arterial blood pressure and heart rate were monitored throughout the experiment as described in the animal preparation section. To compare heart rate easily, delta heart rate was used; this was defined as the difference between heart rate at preinjection (physiologic saline solution or drugs) and that during the period observed.

Analysis of arrhythmias. With the ambulatory ECG monitor, the number of premature ventricular beats during a 2 h period of occlusion was recorded and analyzed by an autoanalyzer (DMC-3110, Nihon Kohden). To express the severity of arrhythmias, the total number of ventricular premature beats, the arrhythmia ratio (defined as the number of ventricular premature beats divided by the total heartbeats) and the total duration time of ventricular tachycardia were used. Ventricular tachycardia was defined as more than three successive ventricular premature beats.

Measurement of mitochondrial function. Two hours after occlusion of the left anterior descending coronary artery, to distinguish the ischemic area from the nonischemic area, Evans blue dye was infused through the femoral vein. Heart mitochondria from the nonischemic area and the ischemic area in each group were prepared by differential centrifugation according to the method of Hatefi et al. (10). The rate of oxygen consumption in state III and the respiratory control index were measured. Oxygen consumption in mitochondria was measured polarographically with an oxygen electrode (UC-12, Central Kagaku) and a closed cell as described previously (11). The incubation medium contained 0.3 *M* mannitol, 10 m*M* potassium chloride, 10 m*M* potassium phosphate, 2.5 m*M* magnesium chloride and 0.25 m*M* ethylenediaminetetraacetic acid, pH 7.4, in a total of 0.7 ml. Respiration was initiated by addition of 0.03 ml of mitochondrial suspension (10 mg protein/ml), and then 0.2 *M* succinic acid (0.03 ml) as substrate and 10 m*M* adenosine diphosphate (0.03 ml) were subsequently added. The rate of oxygen consumption in state III was calculated from mitochondrial oxygen consumption in number of atoms of oxygen consumed per milligram of mitochondrial protein per minute during state III respiration. The respiratory control index was taken as the ratio between the rate of oxygen consumption before and after the addition of adenosine diphosphate.

Measurement of lysosomal enzyme activities. According to the methods of Ruth et al. (12) and Kennett and Weglicki (13), the endocardial tissue from the nonischemic area and the ischemic area in each group was immersed in the extraction medium (0.25 *M* sucrose, 0.6 *M* potassium chloride, 1 m*M* adenosine triphosphate, 1 m*M* ethylenediaminetetraacetic acid and 1 m*M* magnesium chloride, buffered with imidazole at pH 7.2). The tissue was then homogenized with a Teflon pestle tissue grinder. Pellets were obtained by

Table 1. Hemodynamic Effects of Class I Antiarrhythmic Drugs

	−30 min	0 min	30 min	60 min	90 min	120 min
A. Time Course of Systolic Blood Pressure (mm Hg) in All Groups						
Control	104.3 ± 8.9	106.4 ± 6.9	107.9 ± 7.0	110.7 ± 13.4	106.4 ± 15.2	107.1 ± 13.2
Aprindine	114.3 ± 16.2	121.4 ± 11.1	127.9 ± 7.6	127.9 ± 4.9	127.1 ± 7.6	127.9 ± 5.7
Disopyramide	119.3 ± 21.1	104.3 ± 13.4	106.4 ± 25.9	109.3 ± 27.8	107.1 ± 30.9	105.7 ± 33.3
Flecainide	110.0 ± 15.0	105.0 ± 15.3	110.0 ± 20.4	106.4 ± 15.2	104.3 ± 14.6	103.6 ± 17.0
Lidocaine	105.7 ± 10.6	104.3 ± 8.9	108.6 ± 12.5	111.4 ± 12.1	107.1 ± 13.8	104.3 ± 15.4
Mexiletine	116.4 ± 22.3	112.9 ± 25.5	112.1 ± 25.3	110.0 ± 25.4	107.9 ± 23.4	105.0 ± 20.6
Pentisomide	111.4 ± 31.7	107.9 ± 28.4	107.1 ± 21.4	107.9 ± 17.5	109.3 ± 16.2	109.3 ± 15.7
Propafenone	112.1 ± 20.2	109.3 ± 19.7	105.7 ± 19.0	102.8 ± 23.2	100.7 ± 27.5	103.6 ± 28.5
B. Time Course of Diastolic Blood Pressure (mm Hg) in All Groups						
Control	72.4 ± 11.9	73.6 ± 9.4	77.9 ± 8.1	74.3 ± 11.0	73.6 ± 7.5	69.3 ± 9.3
Aprindine	80.7 ± 11.0	82.1 ± 4.9	86.4 ± 8.0	86.4 ± 9.0	87.1 ± 6.4	87.1 ± 7.0
Disopyramide	85.0 ± 13.5	73.6 ± 14.1	72.9 ± 14.7	77.1 ± 15.2	78.6 ± 19.5	74.3 ± 17.9
Flecainide	83.6 ± 12.5	79.3 ± 12.1	80.7 ± 12.4	79.3 ± 9.3	76.4 ± 11.1	77.9 ± 9.1
Lidocaine	73.6 ± 12.5	72.9 ± 7.6	72.1 ± 6.4	72.9 ± 7.6	70.7 ± 9.3	67.9 ± 10.4
Mexiletine	85.7 ± 11.0	80.7 ± 15.9	78.6 ± 13.5	77.1 ± 13.8	75.7 ± 15.7	74.3 ± 14.0
Pentisomide	82.9 ± 26.1	79.3 ± 25.1	80.0 ± 22.5	79.3 ± 19.0	82.1 ± 13.8	81.4 ± 12.8
Propafenone	82.9 ± 15.0	77.1 ± 14.4	76.4 ± 15.5	75.7 ± 15.1	73.6 ± 18.2	75.0 ± 17.3
C. Time Course of Delta Heart Rate (beats/min) in All Groups						
Control		−6.6 ± 9.4	−10.9 ± 11.8	−20.0 ± 11.1	−25.9 ± 12.1	−29.6 ± 13.3
Aprindine		−20.6 ± 10.9	−18.9 ± 14.9	−21.4 ± 15.0	−24.6 ± 16.3	−28.3 ± 14.2
Disopyramide		−32.6 ± 16.2*	−43.3 ± 21.1*	−47.1 ± 23.3†	−50.6 ± 26.6	−54.0 ± 25.7
Flecainide		−30.0 ± 19.9†	−34.3 ± 20.7†	−40.3 ± 21.0	−48.0 ± 21.1	−58.3 ± 28.3
Lidocaine		−8.3 ± 12.7	−8.3 ± 15.6	−12.0 ± 15.5	−19.7 ± 18.9	−29.7 ± 22.6
Mexiletine		−16.0 ± 14.0	−22.9 ± 5.8	−29.7 ± 8.8	−37.4 ± 9.1	−39.1 ± 7.6
Pentisomide		−21.1 ± 18.1	−25.7 ± 19.2	−28.4 ± 20.5	−30.9 ± 21.9	−33.7 ± 23.2
Propafenone		−23.1 ± 18.8	−26.6 ± 18.9	−36.9 ± 22.0	−44.6 ± 25.7	−47.1 ± 27.2

*$p < 0.01$ versus the control group; †$p < 0.05$. Values are mean ± SD; the time of coronary occlusion is expressed as 0 min.

differential centrifugation; the durations in minutes at the various *g* forces were 1,000 *g* for 10 min, 2,500 *g* for 10 min, 9,000 *g* for 10 min, 20,000 *g* for 30 min and 140,000 *g* for 60 min. They were resuspended in 0.25 *M* sucrose containing 10 m*M* imidazole buffered at pH 7.2. All pellets and the final supernatant were assayed for total activity of N-acetyl-β-glucosaminidase and β-glucuronidase with use of the methods of Noto et al. (14) and Kato et al. (15).

Materials. Aprindine hydrochloride, disopyramide hydrochloride, flecainide acetate, lidocaine hydrochloride, mexiletine hydrochloride, penticainide and propafenone were provided by Mitsui Pharmaceutical Co., Ltd.; Chugai Pharmaceutical Co., Ltd.; Eisai Co., Ltd.; Fujisawa Pharmaceutical Co., Ltd.; Behlinger Pharmaceutical Co., Ltd.; Meiji Seika Co., Ltd. and Yamanouchi Pharmaceutical Co., Ltd., respectively. Other chemicals were purchased from Wako Co., Ltd.

Statistics. The significance of all results was determined with the Dunnett's test except for mortality, for which the chi-square test was used. Probability (p) values of <0.05 were considered statistically significant. All data in this study were expressed as mean ± SD.

Results

Of the 61 dogs that underwent coronary artery occlusion, 5 of the 12 dogs in the control group died of ventricular fibrillation and were excluded from the subsequent analysis. No dogs died in the drug-treated groups. Data for the remaining 56 dogs form the basis of the report.

Hemodynamics (Table 1). In the disopyramide and flecainide groups, decreases in heart rate were observed without significant changes in arterial blood pressure. However, neither arterial blood pressure nor delta heart rate in the other drug-treated groups changed significantly from values in the control group throughout the experiment.

Arrhythmias (Table 2). Administration of antiarrhythmic drugs reduced significantly the total number of premature ventricular beats compared with those of the control group. Similar tendencies were observed in the arrhythmia ratio and the total duration of ventricular tachycardia.

Mitochondrial function (Table 3). In the control group, the rate of oxygen consumption in state III in the ischemic area was decreased significantly compared with that in the nonischemic area. A similar tendency was observed in the respiratory control index; that is, a remarkable decrease in

JACC Vol. 14, No. 1
July 1989:219–24

Table 2. Total Number of Ventricular Premature Beats, Arrhythmia Ratio and Total Duration of Ventricular Tachycardia in All Groups

	Total Number of Ventricular Premature Beats	Arrhythmia Ratio (%)	Total Duration of Ventricular Tachycardia(s)
Control	416.4 ± 275.8	2.57 ± 1.85	34.5 ± 47.8
Aprindine	16.4 ± 24.5*	0.07 ± 0.12*	0*
Disopyramide	49.7 ± 53.5*	0.33 ± 0.34*	1.1 ± 2.0*
Flecainide	38.3 ± 39.7*	0.30 ± 0.32*	1.3 ± 3.5*
Lidocaine	12.1 ± 10.4*	0.06 ± 0.07*	0.1 ± 0.2*
Mexiletine	6.0 ± 11.0*	0.03 ± 0.06*	0*
Pentisomide	87.0 ± 41.1*	0.59 ± 0.31*	2.8 ± 2.1†
Propafenone	19.4 ± 25.2*	0.19 ± 0.20*	0*

*$p < 0.01$ versus the control group; †$p < 0.05$. Values are mean ± SD.

the respiratory control index was observed in the ischemic area. In all drug-treated groups, significant improvement of the rate of oxygen consumption in state III in the ischemic areas was observed compared with that of the control group, although these values were lower than those from the respective nonischemic areas. Similar results were observed in the respiratory control index.

Lysosomal enzyme activities (Table 4). In the ischemic area, the activity of N-acetyl-β-glucosaminidase was significantly decreased in the post 9,000 *g* to 140,000 *g* particulate fractions; conversely, the activity of N-acetyl-β-glucosaminidase was increased significantly in the supernatant fraction in the ischemic area. Similar tendencies were observed in the activity of β-glucuronidase in the control group. In all antiarrhythmic drug-treated groups, decreases in the activity of N-acetyl-β-glucosaminidase in the 9,000 *g*, 20,000 *g* and 140,000 *g* fractions and increases in the activity of N-acetyl-β-glucosaminidase in the supernatant fraction in the ischemic area were not observed. Similar tendencies were observed in the activity of β-glucuronidase; that is, administration of antiarrhythmic drugs prevented lysosomal enzyme leakage induced by 2 h coronary occlusion.

Discussion

Mitochondria and lysosomes: cardioprotective effects of class I antiarrhythmic drugs. Myocardial ischemia produces contractile, biochemical and structural abnormalities. Because ischemia causes a decrease in the supply of oxygen and nutrition, there is a consequent marked decrease in energy production in mitochondria with cessation of coronary artery flow. Moreover, because mitochondria exclusively produce high energy phosphate, particularly adenosine triphosphate, maintenance of mitochondrial function is of primary importance for maintaining cellular integrity. Therefore, persistent mitochondrial dysfunction is suggested to lead directly to cellular death (16). Leakage of various lysosomal hydrolytic enzymes might play an important role in the irreversible changes in the ischemic myocardium (17). Hence, estimation of mitochondrial function and leakage of lysosomal enzymes might be useful for assessing myocardial injury after coronary occlusion.

In the present study, mitochondrial function in the ischemic area of the control group was decreased significantly compared with that in the nonischemic area. Leakage of lysosomal enzymes was also observed in ischemic myocardium. Administration of each class I antiarrhythmic drug lessened mitochondrial dysfunction induced by ischemia and prevented leakage of lysosomal enzymes. The myocardial injury associated with acute infarction is ascribed to both ischemia itself and hemodynamic changes. The risk area associated with left anterior descending artery occlusion was estimated to be 30% to 40% (18,19). Experimental ligation of the left anterior descending coronary artery produces a moderate-sized infarct without severe hemodynamic changes, as observed in the present study. No drug significantly changed either systolic or diastolic pressure. No

Table 3. Indexes of Mitochondrial Function in All Drug Groups

	Respiratory Control Index		Rate of Oxygen Consumption in State III*	
	Nonischemic Area	Ischemic Area	Nonischemic Area	Ischemic Area
Control	4.23 ± 0.32	2.39 ± 0.36†	313 ± 31	161 ± 38†
Aprindine	4.25 ± 0.22	3.57 ± 0.36†‡	320 ± 20	241 ± 32†‡
Disopyramide	4.24 ± 0.20	3.36 ± 0.27†‡	328 ± 27	267 ± 24†‡
Flecainide	4.23 ± 0.26	3.29 ± 0.33†‡	326 ± 22	268 ± 20†‡
Lidocaine	4.18 ± 0.16	3.23 ± 0.21†‡	321 ± 26	269 ± 24†‡
Mexiletine	4.24 ± 0.27	3.30 ± 0.37†‡	318 ± 25	252 ± 38†‡
Pentisomide	4.24 ± 0.26	3.41 ± 0.27†‡	312 ± 24	246 ± 37†‡
Propafenone	4.13 ± 0.23	3.43 ± 0.38†‡	324 ± 22	260 ± 37†‡

*n atoms/mg protein/min; †$p < 0.01$ vs. nonischemic area of the corresponding group; ‡$p < 0.01$ versus ischemic area of the control group. All values are mean ± SD.

Table 4. Lysosomal Activities in Control and Drug Treatment Groups

Fraction	1,000 *g*	2,500 *g*	9,000 *g*	20,000 *g*	140,000 *g*	Supernatant
A. Total Activity of N-Acetyl-β-Glucosaminidase (n mol/g wet weight per min) in Myocardial Fraction in the Control Group						
Nonischemic area	114.6 ± 29.8	19.9 ± 5.1	22.4 ± 3.6	21.5 ± 3.6	23.3 ± 2.7	91.1 ± 16.9
Ischemic area	93.2 ± 34.0	13.8 ± 6.6	13.8 ± 5.4*	10.6 ± 2.0*	11.7 ± 3.2*	117.3 ± 14.7*
B. Total Activity of N-Acetyl-β-Glucosaminidase (nmol/g wet weight per min) in Myocardial Fraction in the Ischemic Area in All Groups						
Control	93.2 ± 34.0	13.8 ± 6.6	13.8 ± 5.4	10.6 ± 2.0	11.7 ± 3.2	117.3 ± 14.7
Aprindine	123.7 ± 25.9	15.9 ± 7.0	21.3 ± 5.5†	17.8 ± 6.0*	18.6 ± 5.1*	93.4 ± 7.2*
Disopyramide	109.3 ± 36.1	18.8 ± 2.5	23.0 ± 3.5*	19.3 ± 3.5*	21.8 ± 5.1*	90.9 ± 23.8*
Flecainide	103.8 ± 18.5	18.4 ± 3.3	20.5 ± 2.7†	20.1 ± 3.0*	20.9 ± 3.7*	88.2 ± 13.5*
Lidocaine	111.9 ± 23.0	17.6 ± 1.9	20.5 ± 3.5†	18.4 ± 3.4*	20.9 ± 3.8†	87.0 ± 5.4†
Mexiletine	116.4 ± 27.7	15.6 ± 5.3	22.0 ± 5.1*	19.4 ± 5.3*	18.0 ± 5.3†	90.6 ± 12.4*
Pentisomide	117.9 ± 17.3	18.4 ± 1.4	22.4 ± 5.0*	17.3 ± 3.1†	21.4 ± 3.1*	89.2 ± 11.7*
Propafenone	100.6 ± 10.6	18.3 ± 0.8	22.6 ± 7.8*	21.2 + 3.0*	21.0 ± 1.2*	93.4 ± 13.1*
C. Total Activities of β-Glucuronidase (μg/g wet weight per h) in Myocardial Fraction in the Control Group						
Nonischemic area	83.9 ± 28.9	15.1 ± 5.3	20.0 ± 3.2	20.3 ± 2.9	23.0 ± 3.3	71.3 ± 17.2
Ischemic area	76.1 ± 14.1	8.1 ± 4.8†	12.4 ± 2.8*	10.2 ± 2.0*	10.9 ± 3.3*	108.9 ± 15.5*
D. Total Activity of β-Glucuronidase (μg/g wet weight per h) in Myocardial Fraction in the Ischemic Area in All Groups						
Control	76.1 ± 14.1	8.1 ± 4.8	12.4 ± 2.8	10.2 ± 2.0	10.9 ± 3.3	108.9 ± 15.5
Aprindine	87.5 ± 21.0	14.9 ± 1.9†	19.9 ± 3.9*	17.3 ± 3.9†	17.6 ± 2.7†	77.7 ± 19.2*
Disopyramide	85.7 ± 14.7	14.4 ± 3.7†	18.5 ± 2.8†	19.7 ± 2.5*	18.4 ± 3.1*	81.6 ± 17.6*
Flecainide	89.2 ± 34.9	17.2 ± 3.7*	18.5 ± 3.5†	18.1 ± 2.6*	18.7 ± 4.4*	79.2 ± 17.9*
Lidocaine	74.6 ± 21.5	16.1 ± 4.1*	18.2 ± 2.3†	16.8 ± 4.6†	20.5 ± 3.0*	73.2 ± 6.4*
Mexiletine	85.6 ± 29.1	13.0 ± 4.1	17.9 ± 2.3†	17.5 ± 5.2*	18.0 ± 4.1*	81.7 ± 11.5*
Pentisomide	85.8 ± 19.2	14.6 ± 4.6†	21.8 ± 6.5*	16.8 ± 2.4*	20.4 ± 5.4*	77.2 ± 6.2*
Propafenone	86.4 ± 12.3	13.8 ± 6.3	19.7 ± 3.0*	20.7 ± 4.3*	21.7 ± 3.9*	80.6 ± 12.0*

*$p < 0.01$ versus the control group or ischemic versus nonischemic area. †$p < 0.05$. All values are mean ± SD.

significant changes in delta heart rate except at 0, 30 and 60 min of coronary occlusion in the disopyramide group and at 0 and 30 min in the flecainide group were observed. In addition, we estimated mitochondrial function and lysosomal enzyme activities in ischemic myocardium, which was defined as the area not stained by Evans blue dye. Hence, the beneficial effects of the class I antiarrhythmic drugs used here might be based on the direct cardioprotective effects and not on the improvement in hemodynamic status.

Efficacy of class I antiarrhythmic drugs in ventricular arrhythmias. Ventricular arrhythmias associated with myocardial ischemia may be a severe hazard that cardiologists have to confront in the clinical setting, and many antiarrhythmic agents have been developed. Vaughan Williams (20) classified these antiarrhythmic agents into four categories mainly on the basis of their electrophysiologic properties. Class I type antiarrhythmic agents were classified into three subgroups (21) based on their effect on action potential duration. Disopyramide belongs to class Ia, aprindine, lidocaine, mexiletine and pentisomide to class Ib, and flecainide and propafenone to class Ic. Disopyramide is reported to be effective for treatment of ventricular arrhythmias in patients with suspected acute myocardial infarction (22). Aprindine is also effective in reducing ventricular arrhythmias after acute infarction (23). Lidocaine remains the standard antiarrhythmic drug for ventricular arrhythmias during the coronary care phase of acute myocardial infarction. Koster and Dunning (24) reported that lidocaine, administered by paramedics to patients with suspected myocardial infarction, reduced the occurrence of ventricular fibrillation. Mexiletine is a congener of lidocaine with similar chemical and electrophysiologic properties. Clinical study confirmed the efficacy of mexiletine for ventricular arrhythmias (25). Pentisomide is a well tolerated and effective compound of potential value for treatment of ventricular arrhythmias (26). Flecainide is also a useful compound in patients with life-threatening arrhythmias (27). Propafenone is a unique antiarrhythmic drug and its efficacy in patients with ventricular arrhythmias has been confirmed clinically (28).

Antiarrhythmic action and cardioprotective effect. Regardless of the subclassification of class I antiarrhythmic drugs, every drug used here showed a cardioprotective effect as well as an antiarrhythmic effect. It is well known that intraaortic balloon pumping suppresses ventricular arrhythmias associated with severe ischemia, and these favorable effects might be ascribed to the improvement in the hemodynamic state (29). It is also reported that the severity of ventricular arrhythmias observed in ischemia depends on the extent of necrosis (30). Accordingly, the cardioprotective effect of class I antiarrhythmic drugs observed here might

contribute to their antiarrhythmic effect. The major action of class I antiarrhythmic drugs is based on the inhibition of the sodium channel (31). Jennings et al. (32) reported that sodium and water content increased in ischemic myocardium. From our results, sodium influx might play an important role in the development of ischemia-induced myocardial damage. It is well known that the calcium ion plays an important role in both the genesis of myocardial injury and the development of arrhythmias. It could not be ruled out that class I antiarrhythmic drugs might alter the regulation of intracellular calcium ion such as the release of calcium ion from sarcoplasmic reticulum, although further investigation is necessary to clarify the details.

We should emphasize that every class I drug used here, although differing in subgroup classification, protects myocardium against ischemia, and that administration of class I drugs might favorably alter metabolic changes in patients with acute ischemia because the doses used in the present study are similar to those used clinically.

We express our appreciation to Michael Bodman, a language consultant of our department, for reading the previous draft and making suggestions on language and style.

References

1. Thandroyen FT, McCarthy J, Burton KP, Opie LH. Ryanodine and caffeine prevent ventricular arrhythmias during acute myocardial ischemia and reperfusion in rat heart. Circ Res 1988;62:306–14.
2. Nagai S, Miyazaki Y, Ogawa K, Satake T, Sugiyama S, Ozawa T. The effects of β-blocking agents on mitochondrial function in ischemic myocardium. Jpn Circ J 1984;48:32–6.
3. Muller CA, Opie LH, Hamm CW, Peisach M, Gihwala D. Prevention of ventricular fibrillation by metoprolol in a pig model of acute myocardial ischaemia: absence of a major arrhythmogenic role for cyclic AMP. J Mol Cell Cardiol 1986;18:375–87.
4. Lo HM, Kloner RA, Braunwald E. Effect of intracoronary verapamil on infarct size in the ischemic, reperfused canine heart: critical importance of the timing of treatment. Am J Cardiol 1985;56:672–7.
5. Knabb RM, Rosamond TL, Fox KAA, Sobel BE, Bergmann SR. Enhancement of salvage of reperfused ischemic myocardium by diltiazem. J Am Coll Cardiol 1986;8:861–71.
6. Nokin P, Jungbluth L, Mouton J. Protective effects of amiodarone pretreatment on mitochondrial function and high energy phosphates in ischaemic rat heart. J Mol Cell Cardiol 1987;19:603–14.
7. Nagai S, Miyazaki Y, Ogawa K, Satake T, Sugiyama S, Ozawa T. The effect of coenzyme Q_{10} on reperfusion injury in canine myocardium. J Mol Cell Cardiol 1985;17:873–84.
8. Ruda MYA, Samarenko MB, Afonskaya NI, Saks VA. Reduction of ventricular arrhythmias by phosphocreatine (Neoton) in patients with acute myocardial infarction. Am Heart J 1988;116:393–7.
9. Baron DW, Sunamori M, Harrison CE. Preservation of oxidative phosphorylation by lidocaine in ischemic and reperfused myocardium. Adv Myocardiol 1983;4:567–73.
10. Hatefi Y, Jurtshuk P, Haavik AG. Studies on the electron transport system. XXXII. Respiratory control in beef heart mitochondria. Arch Biochem Biophys 1961;94:148–55.
11. Hieda N, Toki Y, Sugiyama S, Ito T, Satake T, Ozawa T. Prostaglandin I_2 analogue and propranolol prevent ischaemia induced mitochondrial dysfunction through the stabilisation of lysosomal membranes. Cardiovasc Res 1988;22:219–25.
12. Ruth RC, Kennett FF, Weglicki WB. A new technique for isolation of particulate lysosomal activity from canine and rat myocardium. J Mol Cell Cardiol 1978;10:739–51.
13. Kennett FF, Weglicki WB. Effects of well-defined ischemia on myocardial lysosomal and microsomal enzymes in a canine model. Circ Res 1978;43:750–8.
14. Noto A, Ogawa Y, Mori S, et al. Simple, rapid spectrophotometry of urinary N-acetyl-β-D-glucosaminidase, with use of a new chromogenic substrate. Clin Chem 1983;29:1713–6.
15. Kato K, Yoshida K, Tsukamoto H, Nobunaga M, Masuya T, Sawada T. Synthesis of p-nitrophenyl β-D-glucopyranosiduronic acid and its utilization as a substrate for the assay of β-glucuronidase activity. Chem Pharm Bull 1960;8:239–42.
16. Jennings RB, Reimer KA. Lethal myocardial ischemic injury. Am J Pathol 1981;102:241–55.
17. Hearse DJ. Cellular damage during myocardial ischaemia: metabolic changes leading to enzyme leakage. In: Hearse DJ, de Leiris J, eds. Enzymes in Cardiology: Diagnosis and Research. Chichester, New York: John Wiley & Sons, 1979:1–19.
18. Bednar M, Smith B, Pinto A, Mullane KM. Nafazatrom-induced salvage of ischemic myocardium in anesthetized dogs is mediated through inhibition of neutrophil function. Circ Res 1985;57:131–41.
19. Toki Y, Hieda N, Torii T, et al. The effects of lipoxygenase inhibitor and peptidoleukotriene antagonist on myocardial injury in a canine coronary occlusion-reperfusion model. Prostaglandins 1988;35:555–71.
20. Vaughan Williams EM. Characterisation of new antiarrhythmic drugs. Prog Pharmacol 1979;2:13–23.
21. Harrison DC. Antiarrhythmic drug classification: new science and practical applications. Am J Cardiol 1985;56:185–7.
22. Kus T, Sasyniuk BI. Effects of disopyramide phosphate on ventricular arrhythmias in experimental myocardial infraction. J Pharmacol Exp Ther 1976;196:665–75.
23. Pouleur H, Chaudron JM, Reyns P. Effects of disopyramide and aprindine on arrhythmias after acute myocardial infarction. Eur J Cardiol 1977; 5:397–404.
24. Koster RW, Dunning AJ. Intramuscular lidocaine for prevention of lethal arrhythmias in the prehospitalization phase of acute myocardial infarction. N Engl J Med 1985;313:1105–10.
25. Campbell RWF. Mexiletine. N Engl J Med 1987;316:29–34.
26. Priori SG, Bonazzi O, Facchini M, Varisco T, Schwartz PJ. Antiarrhythmic efficacy of penticainide and comparison with disopyramide, flecainide, propafenone and mexiletine by acute oral drug testing. Am J Cardiol 1987;60:1068–72.
27. Somberg JC, Tepper D. Flecainide: a new antiarrhythmic agent. Am Heart J 1986;112:808–13.
28. Karagueuzian HS, Fujimoto T, Katoh T, Peter T, McCullen A, Mandel WJ. Suppression of ventricular arrhythmias by propafenone, a new antiarrhythmic agent, during acute myocardial infarction in the conscious dog: a comparative study with lidocaine. Circulation 1982;66:1190–8.
29. Hanson EC, Levine FH, Kay HR, et al. Control of postinfarction ventricular irritability with the intraaortic balloon pump. Circulation 1980:62(suppl I):I-130–7.
30. Cox JR Jr, Roberts R, Ambos HD, Oliver GC, Sobel BE. Relations between enzymatically estimated myocardial infarct size and early ventricular dysrhythmia. Circulation 1976;53(suppl I):I-150–5.
31. Kodama I, Toyama J, Takanaka C, Yamada K. Block of activated and inactivated sodium channels by class-I antiarrhythmic drugs studied by using the maximum upstroke velocity (V max) of action potential in guinea-pig cardiac muscles. J Mol Cell Cardiol 1987;19:367–77.
32. Jennings RB, Ganote CE, Reimer KA. Ischemic tissue injury. Am J Pathol 1975;81:179–98.